PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70) Rec'd PCT/PTO 29 NOV 2004

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
100707-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE 2003/000858	27.05.2003	31.05.2002
International Patent Classification (IPC) or national classification and IPC		
A61K 9/00, A61K 9/22, A61K 9/52, A61K 47/36, A61K 31/397, A61P 9/00		
Applicant		
AstraZeneca AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.12.2003	24.09.2004
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Eva Johansson/EÖ Telephone No. +46 8 782 25 00

Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY [redacted]ORT ON PATENTABILITY

International application No.
PCT/SE 2003/000858

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY [redacted]RT ON PATENTABILITY

International appl[redacted]ion No.
PCT/SE 2003/000858

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 13

because:

☒ the said international application, or the said claims Nos. 13 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY [redacted]RT ON PATENTABILITY

International application No.
PCT/SE 2003/000858

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-12	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents were cited in the International Search Report:

D1: WO 0219990 A1
D2: WO 9816252 A1
D3: WO 9739770 A1
D4: Bonferoni M C et al; "On the Employment of λ-carrageenan in a Matrix System. II. λ-Carrageenan and Hydroxypropylmethylcellulose Mixtures"; Journal of Controlled Release; 30 (1994) 175-182
D5: Park H-Y et al; "Effect of pH on Drug Release From Polysaccharide Tablets"; Drug Delivery; 5 (1998) 13-18
D6: Talukdar M.M. et al; "In vivo evaluation of xanthan gum as a potential excipient for oral controlled-release matrix tablet formulation"; International Journal of Pharmaceutics; 169 (1998) 105-113

The problem the present application aims to solve is to provide a modified release pharmaceutical formulation comprising a compound of formula (I) as defined in the application.

The scope of the present invention is very broad and comprises, with some exceptions, every imaginable modified release formulation comprising the compounds of formula (I). Claims 1-6 do not explain how such modified release formulations may be achieved.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

Further, according to claim 7 the composition shall comprise a "gelling matrix". It is not clear what this expression includes.
However, in order to be inventive, the claims should clearly define the formulation by its actual composition and the claims should be limited to formulations for which support in the description is to be found.

Documents D1-D3 disclose formulations which comprise or may comprise active agents which are structurally similar to the active ingredient of the present invention. The formulations of D1 are matrices of a modified water soluble polysaccharide, especially hydroxyethyl cellulose. D2 relates to extended release formulations comprising a co-polymer and D3 describes extended release formulations with cyclodextrin. It is considered to be obvious to a person skilled in the art to substitute the active ingredients of D1-D3 for a structurally similar compound such as compound of formula (I) to provide a modified release formulation according to the present invention. The invention according to claims 1-6 and 11-12 is therefore not considered to be inventive.

D1 describes the use of hydroxyethyl cellulose, which in the present application is mentioned as a gelling polymer, in a matrix formulation for modified release of a compound that is structurally similar to the compounds of the invention. Modified release compositions comprising a matrix of a polymer such as HPMC, iota-carrageenan and xanthan gum are well known in the art for example from D4-D6. Sodium dodecyl sulphate is a common ingredient in pharmaceutical formulations. It is considered to be within the skills of a person skilled in the art to use known formulations and known excipients for preparing a formulation of a novel pharmaceutically active agent. As the claims are very general and the application does not show that there is any unexpected technical effect of the formulations according to the invention the invention according to claims 8-10 is considered to lack inventive step.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

Compounds structurally similar to the active compounds of the invention are known from for example D2 and D3 for use in the treatment of disorders characterised by hypercoagulation. It is therefore considered to be obvious to a person skilled in the art to use the compounds of formula (I) in the treatment of cardiovascular disorders. Claims 11-12 are therefore considered to lack inventive step.

INTERNATIONAL PRELIMINARY [redacted]ORT ON PATENTABILITY

International application No.
PCT/SE 2003/000858

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 0244145 A1	06.06.2002	30.11.2001	01.12.2000

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The scope of the present invention is very broad and comprises, with some exceptions, every imaginable modified release formulation comprising the compounds of formula (I). Claims 1-6 do not explain how such modified release formulations may be achieved. The formulation is defined by a desirable characteristic, namely that it should give modified release of the active ingredient, and not by its actual composition. These claims actually formulate the problem, which the present invention aims to solve, rather than a solution to this problem. Claims 1-6 relate to practically any modified release formulation of a compound of formula (I) while the description provides support only for formulations comprising a gelling matrix.

According to claim 7, the composition shall comprise a "gelling matrix". It is not clear what this expression includes. Claims 1-7 and 11-12 are therefore not considered to fulfil the demands of clarity and support as stated in Article 6 PCT. This Statement relates to modified formulations comprising a compound of formula (I) in general but has been focused on formulations comprising a gelling matrix. However, in order to be inventive, the claims should clearly define the formulation by its actual composition and the claims should be limited to formulations for which support in the description is to be found.